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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
HIBBERT, CATHERINE S	

ART UNIT	PAPER NUMBER
1636	

NOTIFICATION DATE	DELIVERY MODE
04/15/2010	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

DocketingDept@young-thompson.com

Office Action Summary	Application No.	Applicant(s)	
	10/532,663	FUCHS ET AL.	
	Examiner	Art Unit	
	CATHERINE HIBBERT	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 January 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *4-24* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *4-24* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicants Amendment to the Claims filed 20 January 2010 is received and entered. Claims 1-3 are cancelled. Claims 4-24 are pending and under consideration in this action.

Response to Amendment

Any objections and rejections not repeated herein are withdrawn.

Initially it is noted that the amendment to the claims filed on 20 January 2010 does not comply with the requirements of 37 CFR 1.121(c) because claim 4, line 12 contains added text (a comma) which was not indicated as new by any markings such as by underlining. However, in the interest of compact prosecution, a phone call to the applicant's representative confirmed that the added comma was an inadvertant error and it was agreed to that the claims are being entered as filed on 20 January 2010 but that the examiner is interpreting the claims in the present action as if the comma was not present.

The applicant is reminded that amendments to the claims filed on or after July 30, 2003 must comply with 37 CFR 1.121(c) which states:

> (c) *Claims*. Amendments to a claim must be made by rewriting the entire claim with all changes (*e.g.*, additions and deletions) as indicated in this subsection, except when the claim is being canceled. Each amendment document that includes a change to an existing claim, cancellation of an existing claim or addition of a new claim, must include a complete listing of all claims ever presented, including the text of all pending and withdrawn claims, in the application. The claim listing, including the text of the claims, in the amendment document will serve to replace all prior versions of the claims, in the application. In the claim listing, the status of every claim must be indicated after its claim number by using one of the following identifiers in a parenthetical expression: (Original), (Currently amended), (Canceled), (Withdrawn), (Previously presented), (New), and (Not entered).

The rejection of claim 21, under 35 U.S.C. 102(b) as being anticipated by Hinds et al is **withdrawn** based on claim amendments.

The rejection of claims 4-5, 10-14, 16-19, 21 and 23 under 35 U.S.C. 102(b) as being anticipated by Ganiatsas et al is **withdrawn** based on claim amendments.

The rejection of Claims 4-21 and 23-24 under 35 U.S.C. 102(e) as being anticipated by Hoeijmakers et al is **withdrawn** based on claim amendments.

Claim Rejections - 35 USC § 102-maintained-in-part

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

The rejection of Claims 4-6, 10-14, 16-18 and 22, under 35 U.S.C. 102(b) as being anticipated by Hinds et al in "Enhanced gene replacement in mycobacteria" (Microbiology, 1999, Vol. 145: p. 519-527, entire document; of record) is maintained for reasons of record and presented herein. The rejection of claim 21 is withdrawn based on claim amendments.

Applicants arguments have been fully considered but are unpersuasive.

The applicant traverses the rejection and argues that the currently amended claim 4 is not anticipated by the cited prior art reference in particular because claim 4 now recites that:

> (1) the target prokaryotic or eukaryotic cell does not comprise the nucleic acid of interest at the target nucleotide sequence prior to transfection;
>
> (2) a DNA vector that is replication competent in the target prokaryotic or eukaryotic cell and comprises the nucleic acid of interest is contacted with a mutagenic agent blocking intracellular DNA replication of said DNA vector, to produce a modified DNA vector; and
>
> (3) transfection of the target prokaryotic or eukaryotic cells is effected with the modified DNA vector and under conditions wherein replication of the modified DNA vector

> commences and insertion of the nucleic acid of interest within the predetermined target nucleotide sequence occurs.

Specifically, the applicant argues that Hinds et al does not anticipate the currently amended claim 4 because the applicants argues:

> The plasmid vectors that are treated with UV radiation in Hinds are suicide vectors, which therefore are not replication competent and do not replicate in the *M. smegmatis* cells into which they are introduced.

Thus, the applicant argues that Hinds fails to disclose:

> at least the following recitations in present claim 4:
> 1. Contacting a DNA vector that is replication competent in the target prokaryotic or eukaryotic cell with a mutagenic agent, to produce a modified DNA vector; and
> 2. Transfecting the target prokaryotic or eukaryotic cells with the modified DNA vector under conditions wherein replication of said modified DNA vector commences.

In addition, the applicant argues that:

> The Official Action calls attention to the third paragraph on page 524 of Hinds, which describes that, in addition to using denatured DNA in a pY6002 vector, the effect of using ss phagemid DNA in a pSYCH09 vector was assessed. However, Table 1 on p. 520 of Hinds confirms that pSYCH09, like pY6002, is a suicide vector, such that neither vector is replication competent in the *M. smegmatis* cells of Hinds, nor does replication of either vector commence in those cells. Moreover, the reference does not disclose that the ss phagemid DNA replicates in the *M. smegmatis* cells of Hinds.

Lastly, the applicant concludes that the Hinds et al reference does not anticipate the disclosed steps that are recited in the method as claimed.

Applicants arguments have been fully considered but are unpersuasive. Hinds et al teach a method comprising contacting a DNA vector (i.e. the replication competent pRAM4 vector) with a mutagenic agent (i.e. UV-irradiation) blocking intracellular DNA replication of the DNA vector to produce a modified vector prior to transformation of the modified vector into target cells and then transfecting/transforming the target cells with the modified of bacterial plasmid vector DNA in order to enhance subsequent homologous recombination in the

mycobacteria (e.g. page 521, right column, last paragraph and page 523 Figure 2 and legend). Hinds et al teach the inactivation of *M. smegmatis* genes and the use of a recombination assay to identify conditions whereby mutagenic agents (i.e. UV irradiation) enhance homologous recombination. Thus, contrary to the applicants assertion that because Hinds et al teach non-replicating suicide vectors and ss phage vectors that the reference therefore does not anticipate the instantly amended claims is not persuasive because, as discussed above, in addition to those non-replication competent vectors, Hinds et al also teaches methods using replication competent vectors and teaches UV treatment prior to transfection of target cells using conditions where replication commences. Thus, Hinds et al anticipates all the limitations of claims 4-6, 10-14, 16-18 and 22.

Therefore, Claims 4-6, 10-14, 16-18, and 22 stand rejected under 35 U.S.C. 102(b) as being anticipated by Hinds et al for reasons of record and above. The rejection of claim 21 is withdrawn based on claim amendments.

New grounds of rejection necessitated by amendment

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* v. *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 4-21 and 23-24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hoeijmakers et al in "Detection Methods Based on HR23 Protein Binding Molecules (US PGPub No:2003/0124605, filed 20 November 2002, which claims priority to Provisional Application No:60/331.773, filed 21 November 2001, see entire document; of record) in view of Hinds et al (above).

Hoeijmakers et al teach a method of targeted homologous recombination using vectors comprising identical 5'- and 3'- sequences respective to the target DNA contained in the chromosome (see especially Figure 1). Hoeijmakers et al teach the use of the mutagenic agents such as UV irradiation and 50 and 100uM concentrations of N-acetoxy-2-acetylaminofluorene (NS-AAF) (p.10, ¶ 132) and wherein the nucleic acid of interest encodes a protein of therapeutic interest, wherein an open reading frame is disrupted by a heterologous nucleotide sequence, and which codes an antisense RNA. For example, Hoeijmakers et al recite:

> An Ola129 mHR23A targeting construct was generated by converting the BglII site in exon II of clone pG7M23Ag1 (containing a 4 kb genomic EcoRI fragment subcloned in pGEM7) into a ClaI site, which (due to a ClaI site in the polylinker) allowed deletion of sequences downstream of the BglII site in exon II (clone pG7M23Ag7). Next, the remaining EcoRI site was removed by filling-in the overhangs with Klenow, resulting in clone pG7M23Ag9. After changing the BstXI site into a SalI site, the 3 kb XhoI-SalI

> fragment was cloned into SalI digested pGEM5, resulting in clone pG5M23Ag17. Next, the 3' arm of the construct, consisting of a Klenow-blunted 1.5 kb SmaI-XbaI fragment starting at the SmaI site in exon VII, was inserted in the blunted NdeI site of pG5M23Ag17 (giving pG5M23Ag20), followed by insertion of a Neo marker cassette in antisense orientation in the ClaI site (giving pG5M23Ag24). Finally, the NotI-NsiI insert of pG5M23Ag24 was recloned into a pGEM-9Zf(-) based vector containing a 2.8 kb thymidine kinase (TK) marker cassette (giving pG5M23Ag30).

In addition, Hoeijmakers et al teach that "cells stably expressing hXPC-GFP/hHR23B were rinsed with PBS, exposed to UV-C light (254 nm; Philips TUV lamp, dose as indicated in the text) and subsequently cultured at 37°C for various time periods (as indicated in the text). XPC was detected either by immunoblot analysis or by visualization in living cells using fluorescence microscopy. A similar approach was used to study the effect of N-acetoxy-2-acetylaminofluorene (NA-AAF, final concentration 50 or 100 μM)"(p.10, ¶ 132), and further teaches mouse and human (HeLa) cells (p.11, ¶ 136 and 141).

However, Hoeijmakers et al fail to teach wherein the DNA vector is treated with the UV prior to transfection into the target cells.

Hinds et al teach methods of homologous recombination and show positive results treating DNA vectors with a mutagenic agent (i.e.UV) prior to transfection into target cells. For example, Hinds et al teach a method comprising contacting a DNA vector (i.e. the replication competent pRAM4 vector) with a mutagenic agent (i.e. UV-irradiation) blocking intracellular DNA replication of the DNA vector to produce a modified vector prior to transformation of the modified vector into target cells and then transfecting/transforming the target cells with the modified of bacterial plasmid vector DNA in order to enhance subsequent homologous recombination in the mycobacteria (e.g. page 521, right column, last paragraph and page 523 Figure 2 and legend). Hinds et al teach the inactivation of *M. smegmatis* genes and the use of a

recombination assay to identify conditions whereby mutagenic agents (i.e. UV irradiation) enhance homologous recombination.

It would have been obvious to one of ordinary skill in the art to combine the method of Hoeijmakers et al with the step of Hinds et al and try contacting the DNA vectors used in methods of homologous recombination of Hoeijmakers et al with the mutagenic agent prior to transfection into the cell because Hinds et al show that this method was successful. One of ordinary skill in the art would have been motivated to do so because Hinds et al show that treating the DNA vectors prior to transfection yielded improved results when compared to treatment in the cell (e.g. page 521, right column, last paragraph and page 523 Figure 2 and legend).

Based upon the teachings of the cited references, the high skill of one of ordinary skill in the art, and absent evidence to the contrary, there would have been a reasonable expectation of success to result when utilizing the method of prior mutagen treatment (as taught by Hinds et al) in the homologous recombination methods of Hoeijmakers et al.

In view of the foregoing, the method of claims 4-21 and 23-24, as a whole, would have been obvious to one of ordinary skill in the art at the time the invention was made. Therefore, the claims are properly rejected under 35 USC *§103(a)*.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 4-24 are rejected under 35 U.S.C. 112, **second paragraph**, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Currently amended independent claim 4 is unclear as to what is encompassed regarding the active method step of part (a) which recites "contacting a DNA vector that is replication competent in said target prokaryotic or eukaryotic cell and comprises the nucleic acid of interest with a mutagenic agent blocking intracellular DNA replication of said DNA vector, to produce a modified DNA vector" because it is unclear whether the active step of contacting a DNA vector with a mutagenic agent must or should occur within a cell or whether the treatment with the mutagenic agent should or could occur outside of a cell. The claim is missing a method step of contacting a cell with the aforementioned DNA vector before modification with the mutagenic agent but the phrase "with a mutagenic agent blocking intracellular DNA replication of said DNA vector" suggests the DNA vector is intended to be contacted with the agent in the cell. Therefore, one of ordinary skill in the art would not be able to ascertain the metes and bounds of applicant's invention.

Claims 5-24 are indefinite insofar as they depend from claim 4.

Conclusion

No claims allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after

the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to CATHERINE HIBBERT, whose telephone number is (571)270-3053. The examiner can normally be reached on M-F 8AM-5PM, EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low can be reached on 571-272-0951. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/NANCY VOGEL/
Primary Examiner, Art Unit 1636

Catherine Hibbert
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